REMARKS

Claim 1 is pending in this application. Claim 1 has been rejected. Claim 1 has been previously amended. Applicants participated in a telephone interview on October 2, 2007. This reply is in response to the Interview Summary dated October 12, 2007 wherein Applicants respectfully point out that the Examiner has failed to mention certain issues discussed and misstated Applicants' position regarding the pending claim and the arguments presented in the Office Action response dated September 19, 2007 which was discussed during the interview.

Claim 1 has been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Although this rejection was only briefly discussed in the telephone interview, it was not listed in the Examiner's summary. As such, Applicants respectfully point out that they continue to disagree with the Examiner's suggestions regarding the teaching of the specification as filed. However, in an earnest effort to advance the prosecution and facilitate allowance of the claim, Applicants amended claim 1 to recite that the dose administered is 1 mg/kg, an amendment presented in the Office Action response filed September 19, 2007 which was the subject of the telephone interview. As stated in the September 19, 2007 response, the limit on a daily dose not to exceed 2

mg/kg/day has been removed and support for the amendment to claim 1 can be found explicitly at page 8, lines 14-15 where it is stated "The dosage of methotrexate shown to be effective in these studies was low, 1 mg/kg." Accordingly, as discussed on the telephone, the claim as amended meets the requirements of 35 U.S.C. 112, first paragraph and withdrawal of this rejection is respectfully requested.

Also not mentioned in the Examiner's Interview Summary is the discussion on the telephone addressing the rejection of claim 1 under 35 U.S.C. 112, first paragraph, with respect to the written description requirement. The Examiner has suggested that the phrase "into the spinal cord but not the brain" is a concept that was not present in the specification as originally filed. As discussed on the telephone, this is not true. As explained in detail in the Office Action response filed September 19, 2007, the basis for the amended claim 1 language "intrathecally into the spinal cord but not into the brain" is clearly within the knowledge of one of skill at the time the application was filed and as such is not required to be explicitly taught in the specification as filed. MPEP 2163 states "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." (Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1384, 231 USPQ at 94). Further MPEP 2163

states that "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." (Vas-Cath, 935 F.2d at 1563, 19 USPQ2d at 1116; Martin v. Johnson, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972)). Therefore, contrary to the Examiner's assertion in the Office Action at page 6, there is no need to incorporate by reference the text of the Human Anatomy and Physiology text because it would have been known to one of skill in the art. Therefore, in amending the language of claim 1, Applicants relied on support found in the general principles of physiology and anatomy that were known at the time the application was filed. As a result, claim 1 as amended meets the requirements of 35 U.S.C. 112, first paragraph. The Examiner had failed to consider that one of ordinary skill in the art would have the understanding of the difference of intrathecal versus intraventricular administration wherein intrathecal administration would by definition result in injection of drug "into the spinal cord but not into brain." She acknowledged this in the telephone interview and even indicated that the claim was allowable since this was textbook knowledge. Accordingly, it was our understanding that this issue was resolved.

Finally, Applicants would like to correct the statements made in the Interview Summary regarding the main issue discussed during the telephone interview, the rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Chamberlain et al. (1998) and Biomethodology of the Rat (http://research.uiowa.edu/animal/print.php?get+rat). The Examiner has suggested in the rejection that Chamberlain et al. teach intraventricular administration of methotrexate at a dose of 2 mg daily (40 mg total dose) to patients with leptomenigeal metastases presenting with radiculopathy, and that the method of administering intrathecally would overlap with this method. Further, the Examiner suggests that the reference on Biomethodology of the Rat teaches that a rat weighs about 250 g and thus the 1 mg/kg dose of the present invention would equate to about 0.8 mg given to a rat, while 2 mg/kg dose of the present invention would equate to about 1.6 mg given to the rat. Therefore, the Examiner suggests these references teach the limitations of claim 1. As discussed in detail during the telephone interview, Applicants disagreed with the Examiner's conclusions regarding the cited references.

In the Interview Summary the Examiner misstates Applicants' position and also has made an error in the dose calculation on the Interview Summary sheet. First, with regard to the teachings of dose and the extrapolation of dose from the teachings of the

specification as filed to compare that dose to the teachings of Chamberlain et al., Applicants respectfully disagree with the Examiner's arguments regarding dose extrapolation from mg/kg body weight doses to mg doses, regardless of body weight. It is a general principle of pharmacology that if an effective dose is taught to be a dose in mg/kg body weight, then in order to extrapolate the dosing from a rat, the species taught in the specification as filed, to a dose that might be used in humans, the species of the Chamberlain et al. reference, the dose extrapolation would be done based on consideration of the difference in body weights, not by ignoring the body weight differences as has been suggested by the Examiner. The contrary is also true. One of skill in the art would never extrapolate from a mg dose in humans to a mg dose in rats without first correcting the mg dose for body weight in humans. This is because of the large difference in size of a human versus a rat. If 2 mg is safe in a very large species (man), that dose could be lethal to a rat, a much smaller species. Instead, dosing would be done by first correcting for body weight. In other words, a 2 mg dose in humans would be 2 mg divided by 60-70 kg body weight which is 0.029 to 0.033 mg/kg/day, a dose much lower than 1 mg/kg as now claimed. The reverse is also true. One of skill would never take a 1 mg/kg dose in a rat and assume that that dose in

mg, about 0.8 mg to the rat, would have efficacy in a human based on the large difference in body size of the human as compared to the rat. The Examiner is totally mistaken in suggesting that one of skill in the art would ignore well-established principles of dose extrapolation and ignore the differences in body size when extrapolating from a rat to humans or even the reverse extrapolating from humans down to rats (as the Examiner is doing in the instant case). In the Interview Summary, the Examiner has incorrectly written a calculation as 1 mg/kg x 2 kg. A rat would NEVER weigh as much as 2 kg. What should be written is 1 mg/kg x 0.2 kg, or 0.2 mg dose, again much lower than is taught in the specification as filed and as claimed.

Further, Applicants wish to correct statements in the Interview Summary regarding dosing on a surface area basis. Although it is true that methotrexate is often dosed on a mg/m2 basis in cancer therapy, this is NOT the case for drugs used to treat pain. This is because, as taught only in the specification as filed, one of skill would need to understand how efficacy related to safety in any particular species. That is why the teaching of the specification as filed is clear in defining dose on a mg/kg basis, to allow one of skill to understand how to extrapolate doses across different species. Chamberlain et al., however, is silent on this issue and thus would not be used by

one of skill to extrapolate from a 2 mg dose in humans, which they would understand to be a dose of approximately 0.029 mg/kg/day based on a 70 kg individual or 0.033 mg/kg/day based on a 60 kg individual, to a dose in a smaller animal such as a rat. The 2 mg dose of Chamberlain et al. is much lower than the dose range claimed in the instant invention and as such would not be obvious to one of skill in the art. Again as well, it must be remembered that it is a general principle of pharmacology that you extrapolate doses across species based on mg/kg not mg alone and not on mg/m2 for pain treatment.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly the reference cited fails to teach or suggest the invention as claimed. The reference cited, in fact, teaches use of methotrexate to treat cancer NOT lower back pain with radiculopathy. Second, the paper teaches use of a much lower dose range and a different route of administration. Therefore, this reference fails to teach the

limitations of the claim as amended and also fails to provide one of skill with an expectation of success. It is only with the specification in hand that one of skill would understand that intrathecal administration at a dose level of 1 mg/kg body weight would be effective for treating lower back pain with radiculopathy. Accordingly, this reference cannot make obvious the invention of the amended claim.

Applicants request correction of the Interview Summary and a fair reconsideration of the Office Action response and telephone discussion with the Examiner. For the Examiner to continue to reject the claim is both legally and scientifically incorrect. Applicants had expected a Notice of Allowance based on the telephone interview. As this response makes clear, the Applicants have clearly met all requirements for patentability. Applicants look forward to a favorable disposition and allowance as soon as possible.

Respectfully submitted,

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